REMARKS

By the present communication claims 8, 16, 27, 35, 52, 55-63, 65 and 73-77 have been canceled without prejudice to pursuing the subject matter of these claims in one or more applications claiming priority to the above-captioned application. New claims 78-80 have been added. Following entry of the amendments claims 1-7, 9-15, 17-26, 28-34, 36-51, 53, 54, 64, 66-72 and 78-80 will be pending and under examination.

Claims 1 and 18 have been amended to recite "wherein said nucleic acid probes are immobilized on a substrate" support for which can be found, for example, in claims 8 and 27, respectively. Claims 1, 18 and 37 have also been amended to recite "amplifying genomic DNA with a population of random primers" support for which can be found, for example, at page 28, lines 17-30; page 32, line 14, through page 34, line 18; and Examples II and IV. Claim 37 and 64 have been amended to recite "wherein said population of genome fragments comprises a high complexity representation," support for which can be found, for example, at page 9, lines 12-24. Claims 13, 19 and 34 have been amended to correct antecedent basis. Claim 64 has been amended to recite "wherein said population of amplified genome fragments is produced by amplification with a plurality of random primers" support for which can be found, for example, in claim 65. Claims 2 and 20 have been amended support for which can be found, for example, at page 9, lines 12-24. Claim 33 has been amended to correct an obvious error. Support for new claims 78-80 can be found, for example, at page 31, line 24, through page 32, line 3. Accordingly, the amendments do not raise any issues of new matter. Therefore, entry of the amendments is respectfully requested.

Claim Objection

Claim 34 was objected to because of apparent improper dependence. Applicants would like to thank the Examiner for pointing out this error. The claim has been amended to depend from claim 18.

Rejections Under 35 U.S.C. § 112

Claims 13 and 19 were rejected under 35 U.S.C. § 112 for reciting terms lacking proper antecedent basis. Applicants would like to thank the Examiner for pointing out these errors. The claims have been amended and now have proper antecedent basis.

Rejections Under 35 U.S.C. § 102

Claims 1-7, 11, 14, 15, 17-20, 22-26, 30, 33, 34 and 36 stand rejected under 35 U.S.C. § 102(b) as allegedly anticipated by Zhang et al., Proc. Natl. Acad. Sci. USA 89:5847-5851 (1992).

Applicants respectfully traverse the rejection. Nevertheless, in order to further prosecution of the application claims 1 and 18 have been amended to recite the language of claims 8 and 27, respectively. Because claims 8 and 27 are not rejected over Zhang et al. the amendment renders the rejection moot. Furthermore, the rejection is moot in regard to the other rejected claims either because they have been canceled or because they depend from amended claims 1 and 18, thereby incorporating the amendments. Therefore, Zhang et al. fails to anticipate the invention as claimed and withdrawal of this ground of rejection is respectfully requested.

Claims 1-3, 7-12, 14, 15, 17, 18, 20-22, 26-31, 33, 34, 36-39, 42-48, 50, 51, 53-54, 64, 66 and 72 stand rejected under 35 U.S.C. § 102(e) as allegedly anticipated by Wigler et al. (US 2004/0137473 A1).

Applicants respectfully traverse the rejection. Nevertheless, in order to further prosecution of the application claims 1, 18 and 37 have been amended to require "amplifying genomic DNA with a population of random primers." Wigler et al. does not describe amplifying genomic DNA with a population of random primers. Rather the amplification methods taught by Wigler et al. rely on a discrete pair of primers that anneal to the same adapter that has been ligated to the ends of genomic DNA fragments (see, for example, paragraphs 49 and 115 of

Wigler et al.). Claim 64 has been amended to recite the language of claim 65. Because claim 65 is not rejected over Zhang et al. the amendment renders the rejection moot. The remaining claims have either been canceled, thereby rendering the rejection moot in regard to those claims, or depend from claims 1, 18, 37 or 64, thereby incorporating the amendments. Therefore, Wigler et al. fails to anticipate the invention as claimed and withdrawal of this ground of rejection is respectfully requested.

Claims 1-3, 6-7, 11, 15, 17-20, 22, 25-26, 30, 33-34 and 36 stand rejected under 35 U.S.C. § 102(b) as allegedly anticipated by Dean et al., Proc. Natl. Acad. Sci. USA 99:5261-5266 (2002).

Applicants respectfully traverse the rejection. Nevertheless, in order to further prosecution of the application claims 1 and 18 have been amended to recite the language of claims 8 and 27, respectively. Because claims 8 and 27 are not rejected over Dean et al. the amendment renders the rejection moot. Furthermore, the rejection is moot in regard to the other rejected claims either because they have been canceled or because they depend from amended claims 1 and 18, thereby incorporating the amendments. Therefore, Dean et al. fails to anticipate the invention as claimed and withdrawal of this ground of rejection is respectfully requested.

Claims 64, 66, 71 and 72 stand rejected under 35 U.S.C. § 102(b) as allegedly anticipated by Pastinen et al., Genome Res. 10:1031-1042 (2000).

Applicants respectfully traverse the rejection. Nevertheless, in order to further prosecution of the application claim 64 has been amended to recite the language of claim 65. Because claim 65 is not rejected over Zhang et al. the amendment renders the rejection moot. Furthermore, the rejection is moot in regard to the other rejected claims because they depend from amended claim 64, thereby incorporating the amendments. Therefore, Pastinen et al. fails to anticipate the invention as claimed and withdrawal of this ground of rejection is respectfully requested.

Rejections Under 35 U.S.C. § 103

Claims 13, 32 and 49 stand rejected under 35 U.S.C. § 103(a) as allegedly obvious over Wigler et al. in view of Maldonado-Rodriguez et al., Mol. Biotech. 11:1-12 (1999). The Office alleges that Wigler et al. describe the method of claims 1, 31 and 48 for the reasons given in the novelty rejection but does not teach contacting the array of nucleic acid probes with chaperone probes. The Office alleges that Maldonado-Rodriguez et al. teaches the use of chaperone probes and that one skilled in the art would have been motivated to use chaperone probes in the method of Wigler et al. to improve hybridization specificity.

To establish a prima facie case of obviousness, three basic criteria must be met: (1) the prior art, either alone or in combination, must teach or suggest every limitation of the rejected claims; (2) the prior art must provide one of ordinary skill with a suggestion or motivation to modify or combine the teachings of the references relied upon by the Examiner to arrive at the claimed invention; and (3) the prior art must provide one of ordinary skill with a reasonable expectation of success. *See Smiths Indus. Med. Sys., Inc. v. Vital Signs, Inc.*, 183 F.3d 1347, 1356 (Fed. Cir. 1999).

Applicants respectfully traverse the rejection because the cited art, either alone or in combination, does not teach or suggest every limitation of the rejected claims. Claims 13, 32 and 49 depend from amended claims 1, 18 and 37, thereby requiring "amplifying genomic DNA with a population of random primers." The Wigler et al. reference does not teach or suggest the claimed method including "amplifying genomic DNA with a population of random primers," for the reasons set forth above in response to the novelty rejection over Wigler et al. Furthermore, the Maldonado-Rodriguez et al. secondary reference does not cure the deficiencies of Wigler et al. because the secondary reference does not teach or suggest "amplifying genomic DNA with a population of random primers." As such, the combination of the two references fails to teach or suggest the invention of claims 13, 32 and 49. Reconsideration and withdrawal of the rejection is respectfully requested.

Claims 40 and 41 stand rejected under 35 U.S.C. § 103(a) as allegedly obvious over Wigler et al. in view of Zhang et al. and further in view of Graves, Trends Biotech. 17:127-134 (1999). The Office alleges that Wigler et al. describe the method of claims 1, 31 and 48 for the reasons given in the novelty rejection but does not teach the use of a low processivity polymerase. The Office alleges that Zhang et al. teaches the use of a low processivity polymerase and that one skilled in the art would have been motivated to use a low processivity polymerase in the method of Wigler et al. to produce smaller target nucleic acids because Graves et al. teaches that smaller nucleic acid fragments are advantageous in array-based hybridization studies.

Applicants respectfully traverse the rejection because the cited art, either alone or in combination, does not teach or suggest every limitation of the rejected claims. Claims 40 and 41 depend from amended claim 37, thereby requiring "amplifying genomic DNA with a population of random primers." The Wigler et al. reference does not teach or suggest the claimed method including "amplifying genomic DNA with a population of random primers," for the reasons set forth above in response to the novelty rejection over Wigler et al. Furthermore, neither Zhang et al. nor Graves et al. taken alone or in combination cure the deficiencies of Wigler et al. because neither reference teaches nor suggests "amplifying genomic DNA with a population of random primers." As such, the combination of references fails to teach or suggest the invention of claims 40 and 41. Reconsideration and withdrawal of the rejection is respectfully requested.

Claims 65 and 67-70 stand rejected under 35 U.S.C. § 103(a) as allegedly obvious over Pastinen et al. in view of Zhang et al. and further in view of Grothues et al., Nucl. Acids Res. 21:1321-1322 (1993). The Office alleges that Pastinen et al. describe the method of claims 64, 66, 71 and 72 for the reasons given in the novelty rejection but does not teach the use of random primers comprising a constant region in the in vitro transcription reaction nor do Pastinen et al. teach replication of the hybridized RNA fragments using locus specific primers. The Office alleges that Zhang et al. teaches a method of primer extension preamplification using random primers and that Grothues et al. teaches a method of amplification using tagged random primers. In regard to claims 65 and 67, the Office alleges that one skilled in the art would have been motivated to use the random primers of Zhang et al. in the genomic amplification method of

Pastinen et al. in order to eliminate the need for optimization of a complicated multiplex PCR. In regard to claims 68-70, the Office alleges that the ordinary user of the method of Pastinen et al. would have been motivated to incorporate constant regions into the random and locus specific primers, thereby enabling an additional amplification reaction using primers complementary to the constant regions, thus providing another level of control over the accuracy of the hybridization results.

Applicants respectfully traverse the rejection. The subject matter of claim 65 has been added to claim 64 by amendment and claim 65 has been canceled. Accordingly, Applicants' arguments will be directed to amended claim 64. Amended claim 64 is directed to a method for detecting typable loci of a genome. The method includes the steps of (a) in vitro transcribing a population of amplified genome fragments, thereby obtaining genomic RNA fragments, wherein the population of amplified genome fragments is produced by amplification with a plurality of random primers, wherein said population of amplified genome fragments comprises a high complexity representation; (b) hybridizing the genomic RNA fragments with a plurality of nucleic acid probes having sequences corresponding to the typable loci, thereby forming a plurality of RNA fragment-probe hybrids; and (c) detecting typable loci of the RNA fragment-probe hybrids.

Claim 64 requires *inter alia* that the population of amplified genome fragments is produced by amplification with a plurality of random primers. The cited references do not teach or suggest modifying the methods of Pastinen et al. to include the use of a plurality of random primers in order to produce a population of amplified genome fragments. Rather, the combination of references suggests that such a modification would be undesirable, as set forth below.

Throughout their article Pastinen et al. point out that their methods provide a one-step method of amplifying DNA and analyzing the amplified product using a microarray. For example, Pastinen et al. state that

> The multiplex PCR products are analyzed on the microarrays without purification, concentration, labeling, or fragmentation in a one-step reaction with all the required enzymes nucleotide analogs, and other reagents. (sentence spanning pages 1032-1033)

Pastinen et al. further points out an advantage of avoiding multiple steps in asserting

> The present method has the significant practical advantage that the post-PCR preparation and the genotyping reaction are combined into a single step, allowing efficient handling of multiple samples in parallel, even without automation. (page 1038, column 1, lines 23-27)

In view of the description in Pastinen et al., those skilled in the art would not have been motivated to modify the methods in such a way as to introduce extra steps and manipulations such as a post-PCR purification step.

However, replacing the multiplex PCR methods of Pastinen et al. with the random primer amplification methods of Zhang et al. or Grothues et al., as suggested by the Office, would introduce a post PCR purification step. Specifically, Grothues et al. describe their T-PCR method as including a spin column gel filtration step to remove unbound primer and primer-primer complexes between the first PCR step and the second PCR step. See page 1321, column 1, second paragraph. Thus, the Grothues method includes at least three separate steps in contrast to the single step method of Pastinen et al. Furthermore, Grothues et al. describe the need for their multiple step amplification method in order to avoid problems associated with random primer amplification such as those described by Zhang et al. In this regard, Grothues et al. describe pilot studies in which the use of random primers for PCR amplification of chromosomal DNA was evaluated and conclude

> Hence most of the DNA amplified by the random primers PCR did not originate from the template DNA, but is the result of primer-primer extension. These results motivated our development of the T-PCR method. (page 1321, column 2, lines 18-21)

With specific reference to the Zhang et al. methods, Grothues et al. assert

> Random 15-mers reportedly did not amplify single cell DNA up to amounts that could be detected on ethidium bromide stained gels (50 PCR cycles)(9). Specific sequences were detected with an additional PCR with pairs of specific primers. This random primer strategy was identical to one of the additional approaches we tried. However the two major problems mentioned above finally led us to abandon this strategy in favor of the T-PCR procedure. (page 1322, column 2, lines 3-10, where reference 9 is to Zhang et al.)

Those skilled in the art would not have been motivated to modify the methods of Pastinen et al. to replace the single step multiplex-PCR methods with the random primer amplification methods of Grothues et al. or Zhang et al. because such a modification would have the undesirable effect of replacing the single-step method of Pastinen et al. with a multi-step process including separate amplification, purification and array analysis steps. Absent any motivation to combine the references they do not render the claimed invention obvious.

Claim 64 also requires *inter alia* that the population of amplified genome fragments comprises a high complexity representation. In contrast, the cited references do not teach or suggest modifying the methods of Pastinen et al to include the use of a population of amplified genome fragments that comprises a high complexity representation. As evident from the title of the article, Pastinen et al. have the goal of providing a system for specific high-throughput genotyping on microarrays. However, Pastinen et al. point out that

> There are two major hurdles for highly parallel screening of SNPs on microarrays. The first is the necessity of amplifying the DNA regions spanning the mutations or SNPs by the PCR to achieve sufficient sensitivity and specificity of detecting single-base variation in the complexity of the human genome limits the capacity of genotyping assays (see page 1032, col. 1, lines 4-10)

Not only do Pastinen et al. question whether detection of SNPs can be sufficiently sensitive and specific in high complexity representations, they also avoid using high complexity representations and instead carry out their studies with amplicon mixtures having low complexity. Specifically, the multiplex PCR methods employed by Pastinen et al. are carried out at a mere 7-8 plex level (see "Multiplex PCR Amplification" section on page 1038). The highest complexity mixture analyzed on an array by Pastinen et al. is a 106-plex mixture produced by spiking 99 non-target PCR products into a mixture of 7 target amplicons (see "Preparation of Templates for Complexity Testing" section on page 1039). In evaluating the effect of this small increase in complexity on their array based detection method, Pastinen et al. observe that "decreased signal intensity is evident with increased template complexity" (page 1036, column 2, lines 10-11). In addition to reducing signal intensity, the presence of the 99 spiked PCR products also affects specificity in the Pastinen et al. method. In this regard, a mixture containing the 99 spiked PCR products, but none of the 7 targets, is included as a control for template-independent extension or cross reaction with non-specific target in Figure 5 (see the sample labeled 99* in the figure). The results of Figure 5 show that the 99 non-target sequences produce non-specific signal intensity on the primer array even when the 7 targets for the primers on the array are absent. A further non-specific effect of the 99 non-target sequences on the primer arrays is that, even in the absence of the 7 target sequences, a ratio indicative of "correct" primer extension over misincorporation is detected.

Turning now to the random primer amplification methods, Zhang et al. teach that amplification using random primers produce high complexity mixtures of genomic DNA fragments. Specifically, Zhang et al. teaches that using their random primer amplification method "it is estimated that at least 78% of the genomic sequence in a single human haploid cell can be copied no less than 30 times" (see page 5847, column 1, first paragraph). Amplification of 78% of the human genome represents an enormous increase in complexity over the 106-plex amplicons mixtures used by Pastinen et al. In view of the description in Pastinen et al. of the hurdles presented by use of high complexity genomic DNA mixtures and the demonstration of reduced sensitivity and specificity when complexity of amplicon mixtures are increased from 7-

plex to a mere 106-plex, those skilled in the art would not have been motivated to modify the method of Pastinen et al. to use an amplicon mixture having a complexity equivalent to 78% of the human genome. Accordingly, those skilled in the art would not have been motivated to replace the low multiplex PCR amplification method of Pastinen et al. with the random primer amplification methods of Zhang et al. or Grothues et al. Absent any motivation to combine the references they do not render the claimed invention obvious. Reconsideration and withdrawal of the rejection is respectfully requested.

Double Patenting

Claims 1-15, 17-34, 36-51 and 53-54 stand provisionally rejected under 35 USC § 101 as allegedly claiming the same invention as claims 1-15, 17-34, 36-51 and 53-54 of co-pending Application US Ser. No. 10/681,800 and as allegedly claiming the same invention as claims 1-15, 17-34, 36-51 and 53-54 of co-pending Application US Ser. No. 11/066,096.

Claims 1-15, 17-34, 36-51 and 53-54 of the present application have been amended and now differ from the claims of co-pending Applications US Ser. Nos. 10/681,800 and 11/066,096. Accordingly, the rejection is rendered moot. Reconsideration and withdrawal of the rejection is respectfully requested.

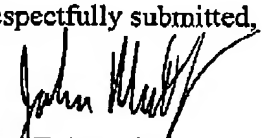
Claims 37, 39-40 and 44-45 stand provisionally rejected under the judicially created doctrine of obviousness-type double patenting as allegedly unpatentable over claims 78-80, 82, 85, 90-94, 96, 104-106, 108, 110 and 115-118 of co-pending Application 10/872,141. Also claims 37, 53 and 54 stand provisionally rejected under the judicially created doctrine of obviousness-type double patenting as allegedly unpatentable over claims 78, 85-86, 104, 110 and 111 of co-pending Application 10/872,141 in view of Wigler et al.

Applicants will consider amending and/or canceling claims in one or both of the applications or filing a terminal disclaimer if necessary and appropriate when there is an indication of otherwise allowable subject matter.

CONCLUSION

In light of the Amendments and Remarks herein, Applicants submit that the claims are in condition for allowance and respectfully request a notice to this effect. The Examiner is invited to call the undersigned agent should there be any questions.

Respectfully submitted,



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